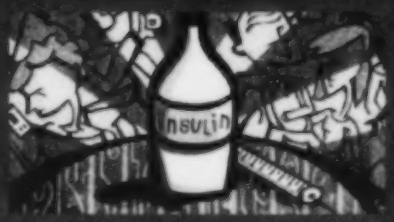
ALBERTA HERITAGE FOUNDATION FOR MEDICAL RESEARCH

ahfmr research news

FALL 2005

On the Cover



Amanda Woodward is an Edmonton-based artist and a graduate of the Alberta College of Art and Design. She loves her work because it allows her to combine her passion for science and medicine with her love of art. Amanda Woodward's images, with her creative and unique vision, appear on the covers of many research publications, including Nature Cell Biology, Nature Medicine, Cancer Cell, Cell Metabolism and Cell.

research news

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AHFMR Mission

AHFMR supports a community of researchers who generate knowledge whose application improves the health and quality of life of Albertans and people throughout the world. AHFMR's long-term commitment is to fund health research based on international standards of excellence and carried out by new and established investigators and researchers in training.

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AHFMR
ALBERTA HERITAGE FOUNDATION FOR MEDICAL RESEARCH

25 YEARS OF EXCELLENCE

Production Notes

Executive editor: Kathleen Thurber
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On the Cover

Amanda Woodward is an Edmonton-based artist and a graduate of the MacEwan design and illustration program. She heads her own design studio, Woodward Design, with her partner and husband, Dana. Some of her illustration clients include Scholastic, the *Edmonton Journal*, *SEE Magazine*, Northern Light Theatre, *Westworld Alberta*, and WIN House.

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AHFMR Visiting Scholar Dr. Hee Yul Ahn's passion for studying the cardioprotective benefits of green tea has taken him to prestigious university laboratories all over the world. Now Dr. Ahn, a professor of pharmacology at Chungbuk National University in South Korea, has landed at the University of Alberta to continue his scientific pursuits. He is in Alberta as part of an international collaboration with Heritage researcher and Canada Research Chair Dr. Sandra Davidge.

Dr. Ahn leans back in his chair, smiling as he thinks back to how he got into the business of studying green tea. "Well, I was born and raised in Seoul, Korea, but I moved to Japan to do my Ph.D. in pharmacology at the University of Tokyo," he says. "It's very interesting because there are several provinces in Japan where the rates of cardiovascular disease are very low. This correlates well with high green-tea consumption—not just one cup of green tea, but several cups every day, whereas in other provinces the opposite is true. So I asked myself, what is it about green tea that has these effects, and what does it do to the cardiovascular system?"

One of the discoveries made by Dr. Ahn was that specific substances in the green tea called catechins (pronounced cat-a-kins) prevent arteries from blocking again following an angioplasty.

"When an artery becomes blocked, or stenosed, a balloon angioplasty is normally done to remove the block. Unfortunately, the blockage may recur for reasons that are not entirely understood," Dr. Ahn explains. "Treatment with green tea catechins prevents this restenosis from occurring." An important discovery, considering that there are no current drug treatments for restenosis.

"What is it about green tea that has these effects?

Dr. Ahn has come to the University of Alberta to work with Dr. Sandra Davidge because he is interested in finding the "why" behind how green tea catechins prevent restenosis. "Dr. Davidge is truly one of the most outstanding vascular biologists in Canada, and I am very excited to have the opportunity to work in her laboratory," he says. Dr. Ahn is using his time in Canada to study the effects of catechins on the endothelium, specialized cells that make up the lining of the blood vessel wall. He has reason to believe that catechins can decrease the expression of specific proteins on endothelial cells that contribute to plaque formation and eventually blockage. The implication is that catechins may prevent atherosclerosis (hardening of the arteries) as well as restenosis—a good explanation for why green-tea lovers have reduced risk for cardiovascular disease.

Catechins prevent arteries from blocking again

Dr. Ahn is also taking some time to soak up his new surroundings. "The research environment at the University of Alberta is so open. People here work together and share space and equipment. Often in

ABOVE: DR. HEE YUL AHN

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research, there is this mentality that you should not help other researchers, because you are competing against them. At the U of A there is a real sense of community, and it's wonderful." Dr Ahn will leave Edmonton in February of 2006 to return to South Korea, but his family will remain in Canada. His eldest daughter will begin her studies at the University of Alberta this fall.

"The research environment is so open"

AHFMR Visiting Scholar Dr. Hee Yul Ahn is a professor of pharmacology in the Department of Medicine at Chungbuk National University in South Korea.

Dr. Sandra Davidge is an AHFMR Senior Scholar and associate professor in the Department of Obstetrics and Gynecology at the University of Alberta. She also holds the Canada Research Chair in Women's Cardiovascular Health.

responding to the reader

"Responding to the Reader" is an AHFMR Research News feature intended to provide up-to-date information on research-related questions, with the help of experts in the Alberta research community. AHFMR cannot provide medical advice, however; please see your family physician about your specific health concerns.

> Heritage researcher Dr. Doug Zochodne is the director of the Neuromuscular Clinic at the University of Calgary, where he sees patients who suffer from diabetic neuropathy. One question Dr. Zochodne hears frequently from his patients is: "Will my nerves grow back?"

Managing blood sugar levels and watching weight aren't the only things people with diabetes have to worry about. Nerve damage (*neuropathy*) is one of the most serious long-term complications of the disease, affecting about half of those with type 1 and type 2 diabetes. Diabetic neuropathy begins in the feet and can extend to the legs and hands, followed in some cases by muscle weakness and paralysis. The condition can be devastating; patients may not be able to walk, and some can no longer work, but because neuropathy has no visible symptoms, family and friends often do not understand. Many patients describe neuropathic pain as a deep, burning, "electrical" type of pain, like painful pins and needles. Yet many people with neuropathy experience no symptoms at all and learn of the condition only when they discover injuries or sores on their feet, injuries that they simply did not feel due to nerve damage and numbness. If unnoticed, these sores can even become gangrenous and lead to amputation of the limb. Diabetic neuropathy can progress with time, and those with severe diabetes are at greater risk.

Diabetic neuropathy can be devastating

As to whether damaged nerves will grow back, the answer is yes–but unfortunately not very well if nerve damage is ongoing or if the nerves must grow a long distance to where they had been originally. The latter may well be the case in diabetic neuropathy,

Insulin is a potent growth factor for nerves

where researchers believe there is a "dying back" of the nerve endings so that they do not supply the feet and the very ends of the toes properly. "We don't have specific ways to reverse diabetic nerve damage—in other words, to make the nerves grow back—and there are no drugs that can stop it in its tracks," he explains, "but nerve regeneration has a lot of potential as a treatment." Peripheral nerves (those that connect muscles to the brain and spinal cord) grow back at the rate of about two or three millimeters per month in humans, depending to some extent on where they are trying to grow. Dr. Zochodne and many of his colleagues continue to test the effects of various growth-factor molecules to stimulate this nerve growth.

Dr. Zochodne also wants to determine why nerve endings retreat and die in neuropathy. In diabetes, small blood vessels become narrow and stiff, thus reducing the blood supply to the nerves. The lack of insulin, or resistance to it, which characterizes diabetes may also contribute to the problem, since insulin is a potent growth factor for nerves.

ABOVE: DR. DOUG ZOCHODNE

Dr. Doug Zochodne is an AHFMR Scientist and a professor in the Department of Clinical Neurosciences at the University of Calgary. *He also receives funding from the Canadian Institutes of Health Research (CIHR); the Canadian Diabetes Association: the Neuropathy Research Fund: and the National Institutes of Health (NIH) in the United States.*

Send us your reader questions!

If we respond to your question in Research News we'll send you an AHFMR t-shirt.

Movement's sixth sense

Have you ever tried to balance on one foot with your eyes closed? No problem you think?

Well, just try it.

As it happens, closing your eyes makes it very difficult to balance on one foot, because it removes some very important sensory information. Balancing is an activity that requires the *proprioceptors*–sensors in the muscles, tendons, and skin. These sensors detect touch, force, and changes in a muscle's length in order to sense movement or sense the position of your limbs. Your ability to maintain the position of your body relies on the normally subconscious ability to combine sensory information from the proprioceptive, visual, and vestibular (the system in the middle ear which senses movements of the head) systems.

"Proprioception is like a sixth sense for the production of movement," explains Heritage Scholar Dr. Kelvin Jones. He investigates the role this sixth sense plays when people must relearn basic movements and motor behaviours after brain injury.

In his investigation, Dr. Jones uses a virtual reality system where the visual and force feedback resulting from movement can be separately altered, so a task such as moving the hand to the right might result in a completely opposite movement onscreen. "The motor command that the brain puts out no longer gives the subjects the output visually that they're sensing from their movements," says Dr. Jones of these experiments. "The brain has to figure out how to reprogram the movements of the arm in order to get the desired outcome. The big problem is that the proprioceptive system and the visual system are giving conflicting information."

Dr. Jones records the neural activity coming from the proprioceptor sensors

To study the adaptation that occurs when people do tasks of this sort, Dr. Jones records the neural activity coming from the proprioceptor sensors in the muscles. He expected to find that the brain makes the sensors fire a lot faster when learning this type of challenging task that delinks the visual and proprioceptive systems. In fact, he discovered the opposite: that those people who can quickly "turn off" their proprioception learn the task more quickly. Meanwhile, those rare people who have lost their proprioceptive fibres due to disease have no problem whatsoever with the tasks because there is no conflict between their visual and their proprioceptive sensory systems.

In another branch of his research, Dr. Jones works on a computer-based tool to help diagnose ALS (amyotrophic lateral sclerosis, also known as Lou Gehrig's disease)–a neurodegenerative disease in which motor nerve cells gradually die. Some of Dr. Jones' interest in restoring movement stems from his days as a grad student, when the case of ALS patient Sue Rodriguez was in the media and before the courts. Faced with the gradual wasting away of her muscles and the certainty of her eventual death, Rodriguez sought the legal right to assisted suicide. She lost the right-to-die battle in the courts, but ultimately took her own life anyway with the help of a doctor. "It was a real bioethics awakening in me in terms of what it would mean to a person who was losing the ability to move," says Dr. Jones. "Sue's case had a real impact on me."

"Proprioception is like a sixth sense for the production of movement"

Dr. Kelvin Jones is an AHFMR Scholar and an assistant professor in the Department of Biomedical Engineering at the University of Alberta. He also receives funding from the Canadian Institutes of Health Research (CIHR) and the Whitaker Foundation.

Selected publications

Stein RB, Gossen ER, Jones KE. Neuronal variability: noise or part of the signal? *Nature Reviews Neuroscience* 2005 May; 6(5):389-397.

Major LA, Jones KE. Simulations of motor unit number estimation techniques. *Journal of Neural Engineering* 2005 April; 2(2):17-34.

ABOVE: DR. KELVIN JONES

Dr. Shirin Bonni is a cancer and basic-science researcher, and passionate about her work. She believes that a family of chemicals called *transforming growth factor-beta* (TGF-β) plays a critical role in controlling cancer development. TGF-β interferes with the growth of certain types of cells, including those in the skin, blood, mammary glands, and digestive tract.

CONTROLLI

When cells become resistant to TGF-β's role in blocking cell division, the body's internal balance is disrupted and cancer may result. Simply put, cancer arises from either an increase in the factors that promote cell growth (*proto-oncogenes*) or a decrease in the factors that inhibit cell growth (*tumour suppressors*).

Born in Kurdistan and educated in Canada, Dr. Bonni moved to Calgary in January 2003 to join the Department of Biochemistry and Molecular Biology at the University of Calgary. She remembers arriving during a most hospitable chinook. "I think it was plus nine degrees the day we arrived. My husband and I were very excited to be here and took the mild weather as a positive sign." Dr. Bonni speaks glowingly about her experiences in Alberta's scientific community, from the professionalism and collegiality of her peers to the dedication of her trainees—and of course, the support she's received from granting agencies.

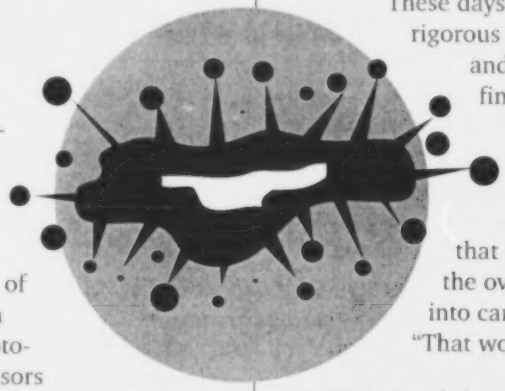
An AHFMR Scholar, Dr. Bonni is pleased with the laboratory and research team she has assembled since coming to the University of Calgary. "I feel so fortunate to be conducting such exciting work with

TGF-β INTERFERES WITH THE GROWTH OF CERTAIN TYPES OF CELLS

NG CANCER

DR. BONNI ZOOMS IN ON THE DETAILS OF INTRACELLULAR MECHANISMS

so many talented people," she says. "The environment is innovative and supportive–there is so much that we can do when we work collaboratively."



Dr. Bonni's current research zooms in on the minute details of intracellular mechanisms, in an attempt to understand how proto-oncogenes and tumour suppressors optimally function and why they become impaired. She employs the techniques of cell biology, molecular biology, and biochemistry to achieve her research goals.

While she was growing up, science came easily to Dr. Bonni and her parents strongly encouraged their children to pursue education. When the family came to Canada in the late 1970s, Shirin Bonni wasted no time in integrating herself into the mainstream school system. "I knew some English when I arrived, so I enrolled in an ESL [English as a second language] program over the summer, and by the fall I entered the local high school." Her academic journey included undergraduate work at the University of Toronto, masters and Ph.D. degrees at Queen's University, and post-doctoral training at the Samuel Lunenfeld Research Institute in Toronto.

These days, Dr. Bonni maintains a rigorous schedule of lab work, teaching, and administration. While she finds it all fulfilling, she admits to being most passionate about cells, their internal mechanisms and their relationship with TGF-β. "I am hopeful that our work will contribute to the overall body of investigation into cancer and its causes," she says. "That would make it all worthwhile."

Heritage Scholar Dr. Shirin Bonni is an assistant professor in the Department of Biochemistry and Molecular Biology at the University of Calgary. In addition to support from AHFMR, she receives funding from the Canadian Institutes of Health Research (CIHR), the Alberta Cancer Board, and the Canada Foundation for Innovation.

Selected publications

Sarker KP, Wilson SM, Bonni S. SnoN is a cell type-specific mediator of transforming growth factor-β responses. *Journal of Biological Chemistry* 2005 Apr 1;280(13):13037-13046.

Konishi Y, Stegmüller J, Matsuda T, Bonni S, Bonni A. Cdh1-APC controls axonal growth and patterning in the mammalian brain. *Science* 2004 Feb 13;303(5660):1026-1030.

LEFT: DR. SHIRIN BONNI

Diabetes research
working toward a cure
insulin

JUST EIGHT MONTHS AGO, Elaine Elyzen was losing her 52-year struggle with severe, uncontrollable diabetes. Although she had meticulously followed doctors' advice, the complications of diabetes were catching up with her. Frequent blackouts, caused by very low blood sugar, made her afraid to go anywhere unless accompanied by someone who knew exactly how to care for her. "I felt guilty because close friends and family always had to be responsible for me. So I stayed in my house and rarely went out."

On March 3, 2005, Elaine's life changed dramatically. An islet transplant replaced the insulin-producing cells that diabetes had destroyed. While she still had to take insulin, it was less than half her regular dose, and her blood sugar was under control. Now, since a second transplant in July, Elaine does not require insulin injections at all.

"It's like I was in a cocoon and now I'm free—physically and mentally. I'm alert. I feel so much better. Life is starting all over for me."

A resident of Claresholm, northwest of Lethbridge, Elaine says there's something special about benefiting from a medical breakthrough that was pioneered here in Alberta. "I've always read up on diabetes, hoping there would be something for me or my daughter, who also has diabetes. My husband and I marvel that the breakthrough was made in our own province."

Elaine is referring to the Edmonton Protocol, a procedure for transplanting healthy islets into patients with type 1 diabetes to regain control of blood sugar. The protocol introduced a unique steroid-free combination of anti-rejection drugs together with a sufficient mass of islets to allow a measure of insulin independence. Islets are the cells in the pancreas that produce insulin—a hormone that helps the body use sugar for energy. (In type 1 diabetes, which is an autoimmune disease, the immune system destroys islets. Type 2 diabetes, which accounts for 90% of all diabetes cases, is not an autoimmune disease and is largely preventable.)

Islets for transplantation are removed from the pancreas of a deceased donor and injected into the recipient's liver, where they begin to release insulin. Recipients must take immunosuppressive drugs for the rest of their lives to stop their immune systems from rejecting the transplanted islets.

The breakthrough was based on years of research into islet transplantation at the University of Alberta. It all began with the formation in 1983 of the Islet Transplantation Group: Dr. Ray Rajotte, Dr. Garth Warnock, and Dr. Norm Kneteman. About 15 years later, Dr. James Shapiro joined the group, and went on to lead the Clinical Islet Transplant Program, the team that first performed the Edmonton Protocol in 1999. Now funded as a Heritage Scholar, Dr. Shapiro and Heritage Senior Scholar Dr. Jonathan Lakey have guided the clinical team to its current success.

Cellular therapy

THE IMPACT of the Edmonton Protocol is evident in the fact that there are now 40 centres in 34 countries doing islet transplantation; globally, more than 550 people have received islet transplants. The Edmonton Protocol is the most successful and widely replicated method of islet transplantation in

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ABOVE: ELAINE ELYZEN

"We're developing the whole area of cellular therapy"

the world. In Alberta, islet transplantation is now considered part of "standard care" for certain patients with type 1 diabetes—patients like Elaine Elyzen.

In November 2001, Dr. Shapiro and his colleagues were awarded a five-year, $22.3-million grant from the Juvenile Diabetes Research Foundation (JDRF) to launch the JDRF Center for Clinical Islet Transplantation at the University of Alberta. Their work is focused on making the Edmonton Protocol safer, more efficient, and more accessible. This includes developing new drug combinations to suppress the immune system without compromising its effectiveness, and developing better methods of harvesting, storing, and preserving islets prior to transplantation. Dr. Jonathan Lakey, head of the Clinical Islet Laboratory, leads the latter research effort.

"Despite the promise of islet transplantation, we face a limiting factor—the number of pancreas donations," explains Dr. Lakey. "Even with the most up-to-date methods for islet isolation and retrieval, it usually takes two pancreases to provide sufficient numbers of islets for one transplant recipient. It is vital that we learn how to maximize every pancreas donation. Isolation procedures have improved immensely, but there is more to be done. We need to increase the yield of islets by keeping donor pancreases in better condition and protecting the islets during the isolation process."

Dr. Lakey's team is exploring new means of islet culture; for example, culturing islets in very low gravity. By improving oxygen delivery to islets and maintaining energy stores within them, their goal is to see transplanted islets survive longer and function better in patients. Another aspect of this work is developing better, more precise tests of islet function, tests that go beyond simply measuring insulin production. The team is investigating several markers of overall islet health, including membrane integrity, apoptosis (programmed cell death), cell-division activity, and oxygen consumption.

Dr. Lakey is applying the knowledge gained from working with islets to other types of tissue, such as cartilage, heart valves, and stem cells. (He is director of Capital Health's Comprehensive Tissue Centre, the largest tissue bank in Canada.) "We're developing the whole area of cellular therapy—transplanting cells and tissues instead of whole organs. The approach has a number of advantages, and it makes sense to capitalize on the expertise we have with islets."

Sources of islets

EVEN WITH IMPROVED ISLET SURVIVAL, there are still far too few donors to supply the demand. That is why Heritage Senior Scholar Dr. Greg Korbutt's research at the University of Alberta

DR. JAMES SHAPIRO

DR. JONATHAN LAKEY

DR. GREG KORBUTT

Cross-species transplantation is controversial

is aimed at developing a larger supply of insulin-producing islets.

One approach is transplanting islets from newborn pigs. Dr. Korbutt's team has been able to reverse diabetes in mice and, more recently, in larger animals with this procedure. "Because this is a preclinical model, it will still be a couple of years before this method can be transferred to humans," he notes, "but the results so far are promising."

Dr. Korbutt acknowledges that cross-species transplantation (known as *xenotransplantation*) is controversial. The dangers include risk of rejection and risk of infection. Risk of rejection can be diminished by using specially bred pigs that have been genetically altered to remove genes that cause rejection. Risk of infection can be addressed with precautions such as raising the pigs in sterile conditions. However, even with a super-clean pig, there is still risk of infection from porcine endogenous retroviruses (PERV)—tiny remnants of viruses scattered throughout the animal's DNA. Dr. Korbutt has completed a study showing that PERV is not transmitted from pig islets into mice. "We need to learn more about this, and that is part of the reason behind preclinical studies. We want to make sure this will be safe for humans."

Another potential source of islets is stem cells, and Dr. Korbutt is also pursuing this line of research. One project involves studying stem cells in the adult pancreas. These cells are capable of becoming islets, and the challenge is to push them to develop in that direction. So far the team has had only limited success. "There's a complex signalling process that pushes stem cells a certain way, and that's what we're trying to mimic," explains Dr. Korbutt. "It's not just a matter of turning a signal on; there are other signals that need to be turned off. Many more studies are needed before we can figure this out."

Tolerance

OTHER DIABETES RESEARCHERS are focusing on the immune system. At the University of Alberta, Heritage Scholar Dr. Colin Anderson is studying tolerance—the mechanism by which the immune system learns to live with certain molecules while at the same time attacking others. Understanding tolerance could be the foundation for helping islet transplant recipients avoid the lifelong use of immunosuppressive drugs. These drugs have long-term side effects which limit the use of transplantation, especially in children.

Is it possible to devise a way for the recipient's immune system to tolerate donor islets? "Our immune system already knows how to develop tolerance; we have to figure how it does it," says

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DR. COLIN ANDERSON

"The immune system knows how to develop tolerance."

Dr. Anderson. Tolerance develops in the thymus, a specialized gland in the upper chest. *T cells* (white blood cells that are critical to the immune response) originate from stem cells in the bone marrow and migrate to the thymus, where they learn how to recognize "self" and "non-self".

Dr. Anderson has made key contributions to understanding T-cell development in the thymus, teasing out factors that control tolerance. Using the results of his basic research, he is designing interventions to develop tolerance. One of them could involve getting donor T cells into the recipient's thymus, which would train the immune system to tolerate the donor's cells. While this is promising in theory, there are huge practical issues to overcome. Such a scheme would require a stem-cell transplant into the bone marrow, which would mean eliminating the recipient's immune response prior to transplant. (This is similar to what is done currently in the case of bone-marrow transplants to treat leukemia.) Dr. Anderson's lab is experimenting with a combination of specially produced antibodies, radiation, and drugs to help donor cells establish in the bone marrow.

At the same time, his team is also developing a new way of encouraging tolerance using "B1B" immune-system cells. Since these cells don't need stem cells to replicate, the stem-cell transplant to shut off the immune response could be avoided. However, it's not yet known whether B1B cells will be effective enough to stimulate tolerance. "We need to try innovative ideas like this because of the problems with immunosuppression," says Dr. Anderson. "The immune system is very complex and doesn't give up its secrets easily."

Genes

AT THE UNIVERSITY OF CALGARY, Heritage Scientist Dr. Pere Santamaria is also wrestling with this complexity. "We know there are more than 20 genes involved in type 1 diabetes. While we know approximately where they are located, we don't know exactly what they are and how they control

DR. PERE SANTAMARIA

both disease susceptibility and disease resistance. In addition, all cells of the immune system are involved in diabetes, and their response is very coordinated. My approach has been to simplify this complexity in order to study diabetes more easily."

Dr. Santamaria's lab has engineered a particular kind of non-obese diabetic (NOD) mouse. (NOD mice develop a form of diabetes very similar to human type 1 diabetes.) The immune system of Dr. Santamaria's NOD mouse has been engineered so that all T cells kill islets. By making genetic variations of this mouse, he can investigate the effects of specific genes. "We want to know more about certain variants of genes, and how they afford resistance or susceptibility. We want to know exactly how the T cells kill the islets, and how the protective variants of genes stop this from happening."

Dr. Santamaria points out that diabetes is not a matter of a single defective gene, as is the case in a disease like cystic fibrosis. The genes that favour diabetes or protect from diabetes are not abnormal genes; rather, they are normal variants that give some selective advantage. "Autoimmunity should be viewed as an unlucky combination of genes that would be good in isolation but are bad in combination," he explains. "The differences between these variants are extremely small, but can cause tremendous differences in susceptibility to disease."

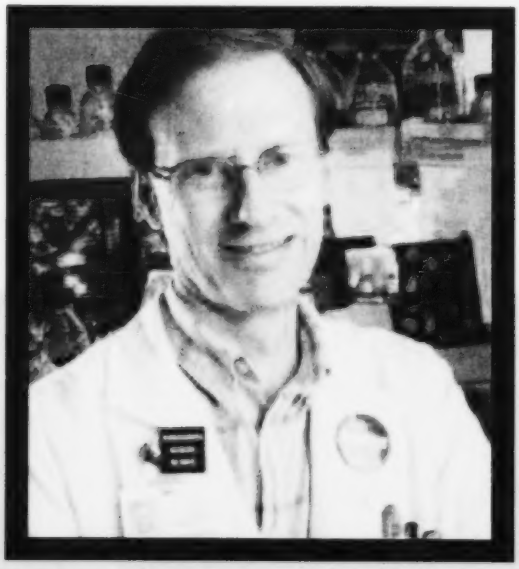
"There are more than 20 genes involved in type 1 diabetes"

Considerable progress has been made in understanding the variants of certain genes linked to diabetes. Dr. Santamaria's team has already identified certain protein interactions that cause diabetes, and shown that his NOD mice are completely protected from the disease when this interaction is blocked. "Promising results like this highlight the need for a better understanding of the pathways that the protective variants of genes use to stop the immune system from destroying cells," he says. "By learning from nature, I'm confident that we can design something intelligently to prevent diabetes."

Disease resistance

SEVERAL OF THE GENES that Dr. Santamaria studies are located in a particular region of human chromosome 6 called the *major histocompatibility complex* (MHC). These genes are key to our ability to resist disease. Like teachers in front of a class, MHC genes make a substance that helps display pieces of foreign invaders—such as bits of virus or bacteria—for their students, the immune cells, to recognize. A colleague of Dr. Santamaria's at the University of Alberta, Heritage Scientist Dr. John Elliott, is studying genetic variations in the MHC.

Dr. Elliott calls the MHC the "Mount Everest of genes" because it is one of the most variable and gene-rich regions of the human genome; it is the place where most of the genetic differences between individuals are found. These differences result in varying abilities to resist disease.



DR. JOHN ELLIOTT

MHC is the "Mount Everest of genes"

For the past five years, Dr. Elliott has participated in an international effort to detail the DNA sequence of the MHC region for two different example genomes associated with diabetes or multiple sclerosis. The MHC Haplotype Project is run by the Wellcome Trust Sanger Institute in the United Kingdom. For the project, Dr. Elliott's lab grew cell lines, prepared DNA, and generated gene libraries. "This project is important because it is analyzing the genome of different individuals in the finest detail. These variations are the difference between being healthy and having an autoimmune disease."

Part of this work involved developing expertise in a number of new DNA cloning technologies, a particular interest of Dr. Elliott's. "We're trying to push the technical edge with this work. It's something I really enjoy. We need a blueprint of the whole MHC to sort out the puzzle of diabetes. That's a huge undertaking—the MHC consists of 4.5 million base pairs. The technology to do this is coming, but it's not there yet. I believe that this understanding will lead to new therapies, perhaps vaccines, that will treat diabetes and other autoimmune diseases."

Dr. Elliott's interest in molecular technologies has also led him to explore the use of gene therapy to improve the islets' chances of survival after transplant. Recent promising results suggest that islets from a single donor pancreas may someday be used to treat two patients with diabetes.

Vision and perseverance

THE BELIEF that there is a better way to treat type 1 diabetes is what drives researchers like Dr. Elliott forward, and when it comes to diabetes research in Alberta, there's no greater believer than the University of Alberta's Dr. Ray Rajotte. He saw the potential for islet transplantation years ago, and

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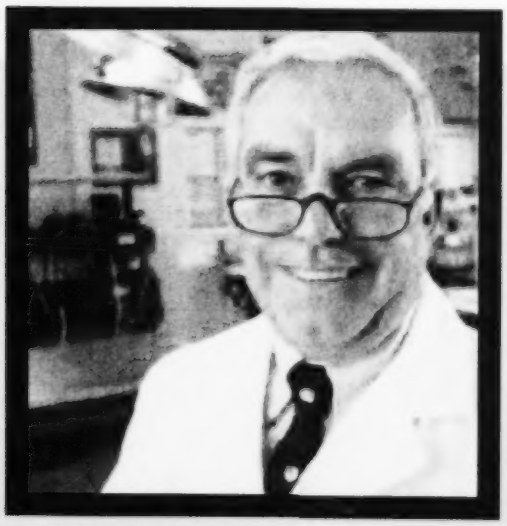
Dr. Rajotte saw the potential for islet transplantation years ago

recognized that this multi-faceted research problem would require a team approach. He set about building the islet transplantation team in 1983, when he first received funding from AHFMR. That team carried out Canada's first islet transplant in 1989. The excellence of the multidisciplinary research team and the success of the Edmonton Protocol is testament to Dr. Rajotte's vision and perseverance. Now his influence has gone beyond islet transplantation, as he is the prime mover behind the creation of the Alberta Diabetes Institute. When construction is finished in 2006, all basic diabetes researchers at the University of Alberta will work under one roof.

"We need a new facility that can house diverse research groups in surgery, exercise physiology, nutrition, epidemiology, immunology, and more," says Dr. Rajotte, who is scientific director of the Alberta Diabetes Institute, as well as director of the Islet Transplantation Group and the Surgical-Medical Research Institute. "The Alberta Diabetes Institute will be a world-class centre that will tackle all aspects of type 1 and type 2 diabetes. In a way, this is the culmination of my career.



DR. RAY RAJOTTE

"What I'm most proud of is the young colleagues who came into my lab and learned about research. They've developed into first-class academic researchers who are now leaders in the field. I looked at this big puzzle of diabetes and knew there was no way I was going to solve it on my own. If you surround yourself with bright, energetic people, you're going to move science forward. And that's exactly what we've done."

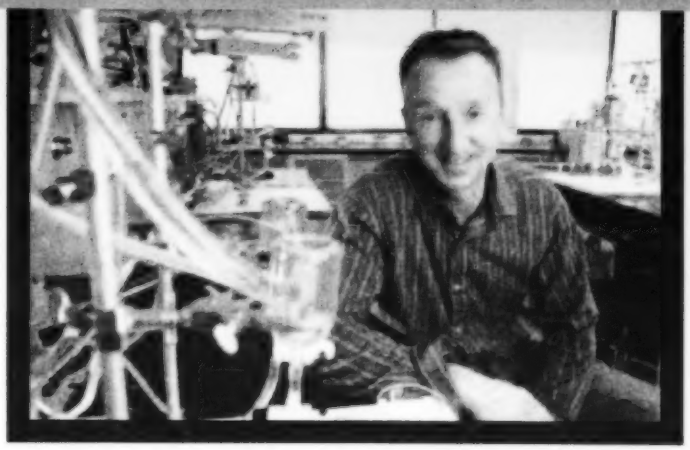
Dr. James Shapiro is an AHFMR Scholar, director of the Clinical Islet Transplant Program, and assistant professor in the Department of Surgery at the University of Alberta. He holds the CIHR-Wyeth-Ayerst Clinical Research Professorial Chair in Transplantation and also receives funding from the Juvenile Diabetes Research Foundation and the National Institutes of Health in the United States.

Dr. Jonathan Lakey is an AHFMR Senior Scholar and an associate professor in the Department of Surgery at the University of Alberta. He is director of the Islet Isolation Laboratory and director of the Comprehensive Tissue Centre for the Capital Health Authority. He also receives funding from the University of Alberta, Capital Health, the Juvenile Diabetes Research Foundation, the Diabetes Research Institute Canada, as well as several private donors to the Clinical Islet Transplant Program.

Dr. Gregory Korbutt is an AHFMR Senior Scholar and an associate professor with the Surgical-Medical Research Institute in the Faculty of Medicine and Dentistry at the University of Alberta. He receives funding from CIHR (Canadian Institutes of Health Research), the Juvenile Diabetes Research Foundation, and the Stem Cell Network.

Dr. Colin Anderson is an AHFMR Scholar and an assistant professor in the departments of Surgery and Medical Microbiology & Immunology, University of Alberta's Faculty of Medicine and Dentistry. He also receives funding from CIHR, the National Institutes of Health in the US, the Edmonton Civic Employees Charitable Assistance Fund, and the Alberta Diabetes Institute.

Dr. Pere Santamaria is an AHFMR Scientist and a full professor and chair of Microbiology and Infectious Diseases in the Faculty of Medicine at the University of Calgary. He is chair and director of the Julia McFarlane Diabetes Research Centre. He also receives funding from CIHR, the Juvenile Diabetes Research Foundation, the Canadian Diabetes Association, NSERC, and the National Institutes of Health in the United States.



DR. PETER LIGHT

New understanding of type 2 diabetes

Heritage Senior Scholar Dr. Peter Light likes to pursue new ideas. So when his work on cardiovascular metabolism brought him into diabetes research, he didn't shy away from the challenge. He embraced it. "It's the new discoveries that keep me going. You take risks, but the payoff can be big."

In this case, the payoff is a better understanding of the risk factors for type 2 diabetes. This form of diabetes used to be called adult-onset diabetes, but nowadays children and teens make up one-third of new type 2 cases. Unlike type 1 diabetes, where the immune system attacks and destroys the insulin-producing islets, in type 2 diabetes the body does not produce enough insulin, or does not use the insulin properly. The causes of this are not fully understood.

Dr. Light's team discovered that people who have a high-fat diet or are overweight may be at increased risk for developing type 2 diabetes if they carry a genetic trait called a polymorphism. This polymorphism affects a specific potassium channel, known as the KATP channel, in the pancreas. (This is the link to Dr. Light's cardiovascular research: his lab specializes in studying the KATP channels in the heart.) When activated, this channel reduces insulin secretion which results in increased blood sugar. This effect is amplified in the polymorphic potassium channel. As it turns out, saturated and trans fats—the so-called 'bad' fats—activate this ion channel much more than polyunsaturated fats (the 'good' fats).

The next step for Dr. Light is to investigate the effect of fats on KATP channels in islets. This work is currently underway.

"Potentially we have a link between diet and genetics," explains Dr. Light. "It seems plausible that people with this potassium-channel polymorphism are more susceptible to type 2 diabetes if they have a high-fat diet or are overweight. In the long term, this could be developed into a screening tool to identify people at risk and then advise them about their diet. There are also anti-diabetes drugs that target this particular ion channel, so they could be prescribed selectively to people with this polymorphism."

Dr. Peter Light is a Heritage Senior Scholar and assistant professor in the Department of Pharmacology, part of the Faculty of Medicine and Dentistry at the University of Alberta. He also receives funding from CIHR, the Canadian Diabetes Association, the Alberta Diabetes Foundation, and the Heart and Stroke Foundation of Canada.

Selected publications

Riedel MJ, Light PE. Saturated and cis/trans unsaturated acyl CoA esters differentially regulate wild-type and polymorphic β-cell ATP-sensitive K^+ channels. *Diabetes* 2005 Jul;54(7):2070-2079.

Riedel MJ, Steckley DC, Light PE. Current status of the E23K Kir6.2 polymorphism: implications for type-2 diabetes. *Human Genetics* 2005 Feb;116(3):133-145.

Dr. John Elliott is an AHFMR Scientist and a full professor in the Department of Medical Microbiology and Immunology in the Faculty of Medicine and Dentistry at the University of Alberta. He chairs the M.D./Ph.D. Committee. Dr. Elliott receives additional funding from CIHR and the Juvenile Diabetes Research Foundation.

Dr. Raymond Rajotte is a full professor at the University of Alberta, director of the Surgical-Medical Research Institute, director of the Islet Transplantation Group, and scientific director of the Alberta Diabetes Institute in the Faculty of Medicine and Dentistry at the University of Alberta. He receives funding from CIHR and the Alberta Diabetes Foundation.

Selected publications

Street CN, Lakey JRT, Shapiro AMJ, Imes S, Rajotte RV, Ryan EA, Lyon JG, Kin T, Avila J, Tsujimura T, Korbutt GS. Islet graft assessment in the Edmonton Protocol: implications for predicting long-term clinical outcome. *Diabetes* 2004 Dec;53(12):3107-3114.

Emamaullee JA, Rajotte RV, Liston P, Korneluk RG, Lakey JRT, Shapiro AMJ, Elliott JF. XIAP overexpression in human islets prevents early posttransplant apoptosis and reduces the islet mass needed to treat diabetes. *Diabetes* 2005 Sep;54(9):2541-2548.

Anderson CC, Chan WFN. Mechanisms and models of peripheral CD4 T cell self-tolerance. *Frontiers in Bioscience* 2004 Sep 1;9:2947-2963.

From bench to bedside to boardroom

More than two million Canadians have diabetes. By the end of the decade, that number is expected to rise to three million. "The number of patients makes diabetes a huge public health issue. It is a tremendous health burden, as well as an economic burden," says Heritage Health Scholar Dr. Jeff Johnson. He chairs the Alliance for Canadian Health Outcomes Research in Diabetes (ACHORD), a multidisciplinary research group based in Alberta.

DR. JEFF JOHNSON

"ACHORD's aim is to provide research which will lead to improved management of diabetes in Canada, from both clinical and health-policy perspectives," explains Dr. Johnson. "Our focus is translational research, which is often described as taking results from basic research and applying them clinically–from 'bench to bedside'. Our work goes one step further–from bench to bedside to boardroom. We want to influence health policy as it applies to diabetes by contributing research evidence that is relevant to policy-makers."

Most of ACHORD's research projects do not focus on diabetes itself, but on the comorbidities (other, simultaneously existing medical conditions) faced by patients. A good example is the Diabetes Outreach Van Enhancement study, which tested a diabetes outreach service for rural physicians. Specialists from Edmonton travelled to two health regions in northern Alberta six times over a six-month period. They presented information to local doctors that focused on improving the management of blood pressure and cholesterol in patients with diabetes. "Although diabetes is considered a sugar disease, it is really a cardiovascular disease, especially type 2 diabetes," notes Dr. Johnson. "About 70% of people with diabetes die of heart attacks and strokes. This is what makes the management of blood pressure and cholesterol so very important."

"We want to influence health policy as it applies to diabetes"

Outcomes such as blood-pressure control and patient well-being were measured and tracked. While they improved considerably in the short term, they began to fall off within a year of stopping the intervention program. On the positive side, Alberta Health and Wellness has asked ACHORD to translate this pilot project into a care-delivery program for the entire province.

Another study was sparked by concerns over the high cost of the supplies used in self-monitoring blood sugar. Although many consider self-monitoring important, there is very little research evidence that it has much of an effect on blood-sugar control. ACHORD designed a randomized-control trial to test whether providing free diabetes-testing strips to people with type 2 diabetes would improve blood-sugar control. This is a key issue across Canada and around the world, as not everyone with diabetes has insurance coverage for these supplies, and governments are frequently called on to provide funding for them. The ACHORD study found that providing free strips to people with type 2 diabetes who are not on insulin did not make a difference in their blood-sugar control.

"Studies like this can help governments decide where to invest healthcare dollars to obtain the best return on that investment," notes Dr. Johnson. "Increasing the funding for self-monitoring supplies will likely reduce the funding available in some other area. Our results suggest that this is not a good balance."

Initially trained as a pharmacist, Dr. Johnson was also a diabetes educator. "Since pursuing an academic career, I've missed the one-on-one interaction with patients–the feeling that you're making a difference. The beauty of my current research is that it involves designing and testing interventions to help populations of people with diabetes. It is research that can truly improve the way we care for people who face this disease."

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Dr. Jeffrey Johnson is a Heritage Health Scholar, chair of the Alliance for Canadian Health Outcomes Research in Diabetes, and a fellow with the Institute of Health Economics. He is an associate professor in the Department of Public Health Sciences, part of the Faculty of Medicine and Dentistry at the University of Alberta. He holds a Canada Research Chair in Diabetes Health Outcomes and also receives funding from the CIHR (Canadian Institutes of Health Research), the Canadian Diabetes Association, the Heart and Stroke Foundation of Canada, the Kidney Foundation, and the Institute of Health Economics.

Selected publication

Johnson JA, Eurich DT, Toth EL, Lewanczuk RZ, Lee TK, Majumdar SR. Generalizability and persistence of a multifaceted intervention for improving quality of care for rural patients with type 2 diabetes. *Diabetes Care* 2005 Apr;28(4):783-788.

Islet transplantation > the Edmonton experience

Every day Edmonton endocrinologist Dr. Edmond Ryan sees people who struggle with diabetes. For most of his patients, he reviews test results, adjusts medication, and treats complications. For a very small number of his type 1 diabetes patients, however, Dr. Ryan can offer something much more dramatic—a procedure that will restore islet function so patients can produce their own insulin. The procedure is islet transplantation.

DR. EDMOND RYAN

"Islet transplantation is for individuals who have severe diabetes that medical therapy cannot control," explains Dr. Ryan, medical director of the University of Alberta's Clinical Islet Transplant Program. "One of my patients told me that the result she hopes for from islet transplantation is to be able to go to bed and not worry about waking up to see a paramedic hovering over her [because a hypoglycemic episode had rendered her unconscious]. This is the kind of person we can help with islet transplantation. It is not for everyone, but it provides a clear benefit to a subset of people with type 1 diabetes."

Dr. Ryan heads a team of clinical specialists who look after islet transplant patients. The team includes nurse coordinators who review lab tests and, with the help of an endocrinologist, adjust medications and watch for complications. Dr. Ryan works with two diabetologists, Dr. Breay Paty and Dr. Peter Senior, in the assessment and follow-up of patients.

As of September 1, 2005, 83 patients had received islet transplants at the University of Alberta Hospital, where the procedure was developed. In a paper published in the scientific journal *Diabetes* in July 2005, the Edmonton team outlined the five-year outcomes for its transplant patients. About 80% were still making insulin, but only 10% had maintained insulin independence. The median duration of insulin independence was 15 months. Those who had to resume insulin therapy required about half the pre-transplant daily dose of insulin, and their blood sugar was in much better control.

"So it's working, but not as well as we'd like," says Dr. Ryan. "The results highlight the huge need for research to understand why people have to go back on insulin. Have some islets died, or are they just not working properly? Are there problems with immune-system suppression? Are there ways to improve the acceptance of the transplanted cells?

"I have phenomenal respect for people who live with diabetes. It's like having a two-year-old child—you think you have him figured out, you turn away, and WHAM, he hits you from behind. Islet transplantation has given people hope that there will be a better way to manage diabetes. I believe the breakthrough achieved in Edmonton, showing that islet transplantation works is an important first step toward the ultimate goal of curing diabetes."

Dr. Edmond Ryan is a full professor in the Department of Medicine at the University of Alberta. He receives funding from the Juvenile Diabetes Research Foundation.

Selected publication

Ryan EA, Paty BW, Senior PA, Bigam D, Alfadhli E, Kneteman NM, Lakey JRT, Shapiro AMJ. Five-year follow-up after clinical islet transplantation. *Diabetes* 2005 Jul;54(7):2060-2069.

outside

"I always knew I was going to do something non-traditional with my Ph.D. I just wasn't sure exactly what that would be."

When Dr. Sarah Lord completed her Ph.D. in experimental surgery at the University of Alberta in January 2005 and began exploring avenues outside the lab, few people understood her desire to leave the academic environment. It wasn't a matter of not enjoying the academic world: "I liked working in the lab, but I felt far removed from the people we were trying to help—people who struggle every day with diabetes." It's a struggle she knows well. Her younger sister has type 1 diabetes. For her Ph.D., Dr. Lord had researched islet cell transplantation, supervised by Dr. Ray Rajotte and Dr. Greg Korbutt, both prominent diabetes researchers and members of the team who pioneered the Edmonton Protocol.

The business world seemed to hold the most potential. She contemplated doing an MBA, but wasn't keen on more schooling. A colleague suggested that she talk to Dr. Diana Shaw, business development manager for Ceapro Inc., an Edmonton-based biotechnology company. That's when things started to click.

After meeting with Dr. Shaw, Dr. Lord was convinced that this would be a good route for her as well. As it turned out, Ceapro had been approved for funding through the AHFMR Technology Commercialization (TC) Internship program, provisional on finding a suitable intern. Dr. Lord applied and was accepted. She began her internship in March 2005.

"Sarah is a highly skilled specialist in the field of diabetes, and Ceapro is delighted to be able to benefit from her expertise through the TC program," says Dr. Shaw. "We're pleased to participate in the business training of Alberta scientists and support the growth of human resources available to biotechnology companies. I believe that together AHFMR and its corporate partners can elevate the position of Alberta as a leader in medical research to include the development and commercialization of new, world-leading technologies. AHFMR's TC program is a critical part of this vision."

At Ceapro, Dr. Lord's focus is moving a new diabetes test-meal technology through the pre-commercialization stage. This technology, called CeaProve, is more accurate than the current test (a liquid glucose drink) at picking up pre-

"AHFMR's TC program is a critical part of this vision"

the lab

CeaProve is more accurate than the current pre-diabetes test

diabetes, a condition that often leads to type 2 diabetes if left untreated. Uncontrolled blood sugar from type 2 diabetes significantly increases the risk of having a heart attack or stroke, as well as the risk of developing kidney failure, blindness, or nerve damage that can lead to amputations. It is estimated that approximately 2.2 million Canadians have diabetes.

Dr. Lord is involved in virtually all aspects of bringing CeaProve to market, including the regulatory process, partnerships, discussions, field studies, and development of marketing materials. "That's the advantage of working for a small company like Ceapro," she says. "We work together closely; I feel like part of the team. The on-the-job learning is great—it's hands-on and practical. This is the ideal situation.

"And while I'm learning business and marketing skills, I can contribute my own skill set to the company. My research and family background give me a different perspective on diabetes. I can ask some of the tough questions that may help get the product to market."

Dr. Lord says the experience she is gaining in technology transfer, commercialization, and small business should make her extremely marketable in the future. In the long term, her "big dream" is to start her own business to benefit people with diabetes.

"The internship has worked out so well for me, I'm eager to get the word out about this career path," adds Dr. Lord. "It's a real option for Ph.D.s. I know so many students who don't want an academic career, and don't necessarily want to do research in a biotech company. Working in technology commercialization is a whole new way to apply your skills."

LEFT: DR. SARAH LORD

ABOVE: DR. SARAH LORD AND DR. DIANA SHAW

TC internship: The details

AHFMR's Technology Commercialization (TC) Internship program has already had an important impact on building the biotechnology and health industries in Alberta. Since 1996, 28 knowledgeable and talented young scientists and entrepreneurs have been trained in the program. The majority of them are working in technology transfer or technology commercialization positions. There are currently 10 interns in the program. Internships are for one year, renewable for an additional year.

TC internship applicants must hold, or be in the final year of study for, a degree in business, management, or science. They must also be sponsored by an Alberta organization engaged in enhancing the commercialization of medical or health-related technology.

The companies take on the responsibility of training the interns in aspects of commercialization relative to their core businesses. Receptor companies choose their interns, selecting candidates who possess skills, knowledge, and attributes that will contribute effectively to the company's bottom line. This customized approach ensures that the partnership formed between the sponsoring company and the intern will add value to the internship and enrich the experience for both parties.

Motor function in diabetes

Noor Ramji, like her identical twin sister Nasreen, is living her dream. Both want to be doctors. Born in Calgary and raised in Toronto, the two young women graduated a few years ago from Queen's University in Ontario with bachelor degrees in life sciences. Now both are medical students. Noor is a first-year medical student at the University of Calgary; her dream is to become a clinician-scientist with a special interest in neurology and neuroscience. Her sister, in medical school in Ontario, hopes to become a family physician.

"I love it here," says Ramji. "I'm really glad I made the choice to come to Calgary. It seems like all my dreams have come true."

Noor Ramji's dreams certainly seem on track. Several years ago she won a neuroscience award to attend the University of Calgary. She also received a Heritage trainee award. She began her master's thesis in 2003 and in September 2005 started medical school. She is now studying for her medical degree while also working to complete her master's degree in the research laboratory of Heritage Scientist and consultant neurologist Dr. Douglas Zochodne (see story on page 2).

Motor nerve cells seem to be spared in early diabetes

Ramji studies motor function in diabetes. People with chronic diabetes may ultimately suffer damage to the peripheral nerves in their extremities, she explains. The damage develops slowly but worsens progressively, until it finally causes irreversible sensory

NOOR RAMJI

loss. But studies suggest that people with diabetes maintain motor function longer than sensory function. Ramji has found that, in comparison with sensory nerve cells, the form, structure, and number of motor nerve cells seem to be spared in early diabetes. She hopes that improved knowledge of the motor system in diabetes will reveal ways to prevent irreversible damage to the sensory nervous system.

"All of my role models have been clinician-scientists"

"It seems like the motor neurons have a defence mechanism that may be protecting them in long-term diabetes," she says. "If we can take whatever the motor neurons are doing to protect themselves and apply it to the sensory side, we may be able to prevent the sensory deficits. We may even be able to extrapolate this to Lou Gehrig's disease [amyotrophic lateral sclerosis] and other models where motor neurons are targeted but other neurons are spared."

Ramji is currently trying to decide if she will pursue a place in the University of Calgary's joint M.D./Ph.D. program after completing her master's degree. "I do have a passion for research," she says. "All of my role models have been clinician-scientists like Dr. Zochodne. He's a wonderful role model. He shows that you can actually do research and medicine at the same time, and do it well. That's inspiring. There are a not a lot of physicians out there who do that. That's why I came to Alberta. This is where you can do both medicine and research. Alberta researchers and students are lucky. It's fabulous here for research."

AHFMR Student Noor Ramji is an M.Sc. student and medical student at the University of Calgary. She also receives funding from NSERC (Natural Sciences and Engineering Research Council of Canada).

Responding to the reader

Calgary Neuropathy Support Group
http://www.calgarypners.org

Movement's sixth sense

Clinical and Theoretical Neuroscience Laboratory
http://www.ualberta.ca/~kejones/

Controlling cancer

Dr. Shirin Bonni's web page
http://www.fp.ucalgary.ca/bmb/bonni/bonni.html

Diabetes research: working toward a cure

Canadian Diabetes Association
http://www.diabetes.ca

University of Alberta Clinical Islet Transplant Program
http://www.islet.ca

Juvenile Diabetes Research Foundation
http://www.jdrf.org

Alliance for Canadian Health Outcomes Research in Diabetes
http://www.achord.ca

A science career outside the lab

Ceapro Inc.
http://www.ceapro.com

2005 AHFMR Media Fellows

Every summer, AHFMR selects one student from the University of Alberta and one from the University of Calgary for a unique opportunity with an Alberta media outlet. The AHFMR Media Fellowship program allows participants to spend 12 weeks reporting on science stories—as reporters, researchers, or production assistants. Not a bad summer job! Below, the 2005 Media Fellows describe their experiences at CBC radio this past summer.

Tara Narwani, Ph.D. student, University of Alberta

Every day there was a new challenge to be met at CBC. Learning the language of the workplace; cold-calling people for interviews; writing stories on deadline; and voicing my own story for the news—an absolute thrill! I realized that my scientific training has given me something valuable to offer outside of a laboratory setting.

A couple of stories I worked on were particularly challenging and rewarding. One was about research into the increasing incidence of pre-term births in Alberta. The second dealt with a thermodynamic approach to cryofreezing tissue for transplant.

For every story, the challenge is to convince listeners that it's important to their lives and to capture their imagination. So often I've heard the complaint that scientists can't communicate the importance of their work to the public. This program has certainly taught me how a good science story is told. I feel I'm better equipped to talk about my own research now that I'm about to plunge back into it.

Branko Lazarevic, B.Sc. student, University of Calgary

The AHFMR Media Fellowship turned out to be an amazing experience. This program is one of the few opportunities for science students to communicate cutting-edge research and address issues that have a tremendous impact on society.

On my third day on the job, I was asked to cover a press conference at the University of Calgary announcing a $3-million donation to multiple sclerosis researchers. The clip I put together ran on the 5:30 news that same day. It was a real thrill listening to that first report. I was also able to generate a discussion about the massive cost of new cancer treatments. The director of the treatment approval committee with the Alberta Cancer Board came to the studio to discuss the issue, generating a talkback line. I met researchers who are passionate not only about their research but also about the welfare of their patients. Like Dr. Paolo Federico, a clinical neuroscientist at the Foothills Hospital, whose MRI research provides more precise and effective surgical solutions for patients who suffer from seizures.

LEFT: TARA NARWANI AND ABOVE: BRANKO LAZAREVIC

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LEFT: TARA NARWANI AND ABOVE: BRANKO LAZAREVIC

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